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Antifibrinolytic Drugs and Perioperative Hemostasis

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Although excessive bleeding is widely recognized as a common complication of cardiac surgery, the recent success of antifibrinolytic drugs as prophylactic hemostatic agents has received little attention outside the surgical literature. The etiology of the coagulopathy following cardiac surgery is clearly multifactorial; however, the success of antifibrinolytic drugs as hemostatic agents suggests that fibrinolysis contributes to bleeding in this setting. Increasingly widespread administration of these drugs necessitates increased awareness of the risks and benefits posed by perioperative antifibrinolytic therapy. The objectives of this review are to understand the mechanisms of action of antifibrinolytic drugs in the context of the normal hemostatic response and to review evidence pertaining to the efficacy and safety of antifibrinolytic drugs as hemostatic agents during cardiac surgery. Am. J. Hematol. 56:32–36, 1997. © 1997 Wiley-Liss, Inc.

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INTRODUCTION

Under normal conditions, fibrinolysis provides an important mechanism to limit propagation of intravascular thrombosis. Tissue plasminogen activator (t-PA), released from vascular endothelium, converts plasminogen to plasmin, the active mediator of fibrinolysis [1]. Plasmin impairs the hemostatic process by a number of mechanisms including degradation of cofactors Va and VIIIa, proteolysis of platelet adhesive receptors, consumption of α2-antiplasmin, and the degradation of fibrin and fibrinogen [2]. Numerous investigations have identified increased fibrinolytic activity in association with cardiac surgery. In fact, in patients undergoing cardiac surgery Tanaka and colleagues [3] demonstrated a direct relationship between plasma concentrations of t-PA and duration of cardiopulmonary bypass (CPB). Other investigators have observed increased concentrations of fibrin(ogen) degradation products and D-dimer during CPB, additional evidence of fibrinolytic activity [4]. The mechanism by which t-PA is released during CPB remains unclear. Failure to suppress thrombin and fibrin generation may play a role. Thrombin is a potent stimulant for the release of t-PA from vascular endothelium, and fibrin potentiates the generation of plasmin from the zymogen precursor plasminogen [5,6]. Our laboratory and others have demonstrated that substantial concentrations of thrombin and fibrin are generated throughout the period of CPB [7,8].

ANTIFIBRINOLYTIC DRUGS

At present, three antifibrinolytic drugs are commercially available for clinical administration: the synthetic lysine analogs, epsilon-aminocaproic acid (EACA) and tranexamic acid, and the natural serine protease inhibitor, aprotinin (Table I). Aprotinin was initially isolated in 1930 [9] with development of the synthetic antifibrinolytics EACA and tranexamic acid reported in 1957 and 1962 [10,11], respectively; however, only in the past decade have the blood sparing effects of these agents achieved widespread recognition and application.

As lysine analogues, both EACA and tranexamic acid suppress fibrinolytic activity by competitively inhibiting the binding of plasminogen and plasmin to fibrin. By

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TABLE 1. Antifibrinolytic Therapy*

Drug	Source	Molecular weight (daltons)	Structure	Mechanism of action	Terminal elimination half-life (hr)	Excretion	Standard dosing regimens for adult cardiac surgery	Hospital cost (standard dosing regimens for CABG surgery)
ε-Amino-caproic acid	Synthetic	131	6-aminohexanoic acid; lysine analog	Competitive inhibitor of plasmin(ogen) binding	2	Renal	Loading dose 150 mg/kg Maintenance 15 mg/kg/hr	$11–30
Tranexamic acid	Synthetic	157	trans-4-(amino-methyl)cyclo-hexane carboxylic acid; lysine analog	Competitive inhibitor of plasmin(ogen) binding	2	Renal	Loading dose 15 mg/kg Maintenance 1.5 mg/kg/hr	$30–100
Aprotinin	Bovine lung	6,512	58 amino acid peptide	Broad spectrum serine protease inhibitor; binds active site	2	Renal	Loading dose 280 mg Maintenance 70 mg/hr CPB pump prime 280 mg	$800–1,100

*CABG: coronary artery bypass graft.

blocking access to the fibrin template, these drugs substantially decrease the kinetic rate of plasmin formation as well as the plasmin-mediated degradation of fibrin and fibrinogen [12].

Owing to the limited number of investigations with the synthetic antifibrinolytics, optimal dosing regimens for EACA and tranexamic acid remain controversial. In order to achieve antifibrinolytic concentrations in plasma, estimated at 0.01 mol/L, EACA must be administered in an intravenous loading dose of 150 mg/kg followed by a continuous infusion of 15 mg/kg/hr [13]. Given that the potency of tranexamic acid has been estimated as approximately 10-fold greater than EACA [14,15], tranexamic acid typically is administered as a loading dose of 15 mg/kg, followed by a continuous infusion of 1.5 mg/kg/hr. The initial elimination half-life of both synthetic antifibrinolytics is approximately 1–1.5 hr, and these drugs must be administered by continuous infusion in order to maintain therapeutic drug concentrations throughout the perioperative period. The synthetic antifibrinolytic drugs are concentrated within the urine with over 80% of the administered dose being excreted in an active unaltered form during the initial 12 hr following administration [13].

Both EACA and tranexamic acid have proven efficacious in reducing bleeding after cardiac surgery. Generally, randomized prospective trials report 30–40% reductions in blood loss compared to placebo control groups [16–20]. Prior investigations suggest that antifibrinolytics must be administered prior to the fibrinolytic stimulation of CPB in order to achieve a hemostatic effect. Administration of the synthetic antifibrinolytics following completion of CPB has resulted in only limited reductions in bleeding [21,22].

As opposed to the synthetic antifibrinolytic drugs, aprotinin is a naturally occurring broad spectrum serine protease inhibitor. Initially isolated from bovine lymph nodes, aprotinin consists of a 58 amino acid polypeptide chain, molecular weight 6,512 daltons, with inhibitory activity toward plasmin, kallikrein, and trypsin [23]. Aprotinin forms reversible inhibitory complexes with the active site serine of multiple target proteases including components of fibrinolysis, complement, kinin generation, and the intrinsic pathway of coagulation. Further evidence suggests that aprotinin provides a platelet ''protective'' effect with preservation of surface glycoprotein receptors [24]. The initial elimination half-life of aprotinin is approximately 1.5–2 hr, and as with the synthetic antifibrinolytics elimination occurs primarily by renal excretion [13].

Although a variety of dosing regimens have been reported with aprotinin, the most efficacious and widely accepted has been that of the ''high dose'' or ''Hammersmith'' regimen [25]. Frequently described in kallikrein inactivator units (KIU), with 100,000 KIU being equivalent to 14 mg or 2.15 μmol/L of pure aprotinin [13], the ''high dose'' regimen comprises a loading dose of 2×10^6 KIU (280 mg) followed by a continuous infusion of 5×10^5 KIU (70 mg) per hour. An additional 2×10^6 KIU (280 mg) is added to the circuit of the CPB pump in order to compensate for hemodilution occurring upon initiation of CPB.

Numerous investigations have demonstrated the efficacy of aprotinin in decreasing blood loss after cardiac surgery. Using a high dose regimen of aprotinin, 30–50% reductions in bleeding after cardiac surgery are consistently achieved [25–28]. Furthermore, aprotinin has been demonstrated to reduce blood loss in high-risk settings

TABLE 2. Antifibrinolytic Comparative Investigations*

Author	Publication date	Surgical procedures	Randomized subjects per cohort	Postoperative blood loss
Trinh-Duc et al. [32]	1992	Primary CABG Valve replacement preoperations	29	No difference
Cousin et al. [33]	1993	Primary CABG Valve replacement preoperations	20	No difference
Blauhut et al. [34]	1994	Primary CABG	14	No difference
Boughenou et al. [35]	1995	Primary CABG Valve replacement preoperations	17	No difference
Speekenbrink et al. [36]	1995	Primary CABG	15	No difference[a]
Pugh and Wielogorski [37]	1995	Primary CABG	21	No difference[a]
Penta de Peppo et al. [38]	1995	Primary CABG Valve replacement	15	Aprotinin most effective
Menichetti et al. [39]	1996	Primary CABG	24	Aprotinin most effective

*CABG: coronary artery bypass graft.
[a]"Low dose" aprotinin therapy (total dose 280 mg).

such as reoperations, bacterial endocarditis, and patients receiving aspirin [29,30].

COMPARISONS AMONG ANTIFIBRINOLYTIC DRUGS

Whether one antifibrinolytic provides better hemostasis than another remains to be determined. At present, wholesale cost for the standard ''high dose'' regimen of aprotinin (Trasylol™) is approximately $1,080 per patient as compared to $11 per patient for epsilon aminocaproic acid (Amicar™) [31]. Available evidence suggests that both the synthetic antifibrinolytic drugs and aprotinin decrease bleeding associated with cardiac surgery. In fact, the majority of prospective randomized trials to date comparing the hemostatic efficacy of aprotinin with synthetic antifibrinolytics have failed to demonstrate statistically significant differences in blood loss for patients receiving one antifibrinolytic as opposed to another (Table II) [32–39]. Furthermore, a metaanalysis of cardiac surgery antifibrinolytic trials demonstrated significant reductions in bleeding and transfusion requirements for both the synthetic antifibrinolytics and aprotinin [40].

COMPLICATIONS ASSOCIATED WITH ANTIFIBRINOLYTIC THERAPY

Much of the controversy surrounding antifibrinolytic drugs has centered on their potential for promoting pathologic intravascular thrombosis. Case reports, pertaining to both EACA and aprotinin, have described excessive thrombus formation on pulmonary artery catheters in patients receiving antifibrinolytic therapy [41,42]. Of even greater concern was a report by Cosgrove and associates [43] describing a trend toward increased perioperative myocardial infarction in patients receiving aprotinin. Subsequent prospective studies directly assessing postoperative coronary graft patency following aprotinin administration failed to demonstrate adverse effects on either graft patency or postoperative mortality [44–46].

Reports of intraoperative thrombosis in association with aprotinin therapy may relate to failure to provide adequate intraoperative anticoagulation during CPB. Aprotinin-mediated inhibition of kallikrein, and therefore the intrinsic pathway of coagulation, results in artifactual prolongation of both the activated coagulation time (ACT) and the activated partial thromboplastin time (aPTT) [47]. Although aprotinin inhibits the intrinsic pathway, tissue factor and the extrinsic pathway—primary mediators of in vivo coagulation—remain unaffected. Failure to recognize the effects of aprotinin on laboratory monitoring of anticoagulation may result in inadequate intraoperative heparin administration. If the ACT is to be used for monitoring anticoagulation in the presence of aprotinin, a recommended approach, would be to increase the acceptable minimal ACT value (>750 sec using a celite activator) or alternatively to substitute a kaolin-based ACT in place of celite. Kaolin-based ACT measurements are less sensitive to the effects of aprotinin, presumably because of the ability of kaolin to bind aprotinin in solution [48].

A second area of concern with the antifibrinolytic drugs relates to their potential effects on renal function. In particular, an investigation by Sundt et al. [49] described an association between administration of aprotinin and postoperative renal failure in patients undergoing thoracoabdominal aortic aneurysm resection with deep

hypothermic circulatory arrest. As with the report by Cosgrove et al. [43], failure to provide adequate intraoperative anticoagulation in the presence of aprotinin would appear to be the most likely explanation for these complications. Prospective randomized trials failed to detect significant adverse effects of aprotinin on postoperative renal function in patients undergoing cardiac surgery [43,50]; however, further investigations are needed to clarify the role of antifibrinolytic therapy in the setting of deep hypothermic circulatory arrest.

One final concern relates to the potential for anaphylactoid reactions following aprotinin. As a naturally occurring protein, aprotinin induces an immunologic response following administration. As many as 50% of patients receiving high-dose aprotinin develop specific IgG antibodies within 3 months of exposure, and over half of these patients continue to test positive for the antibody 4 years following the initial exposure [51,52]. Diefenbach et al. [53] recently reported a fatal episode of anaphylactic shock following reexposure to aprotinin. The manufacturer estimates a 0.5% overall risk of anaphylactoid reactions following exposure to aprotinin; however, this risk may increase to 6–9% following reexposure [54–56]. These findings tend to argue against more widespread use of aprotinin in the perioperative setting and suggest that this therapy should be reserved for procedures at particularly high risk for bleeding such as repeat coronary artery bypass graft surgery and complicated valvular replacements.

SUMMARY

Both the synthetic antifibrinolytic drugs and aprotinin inhibit fibrinolytic activity and bleeding during cardiac surgery. Furthermore, use of these drugs does not appear to pose a major risk of perioperative thrombosis. The relative safety of antifibrinolytic drugs in the setting of cardiac surgery may relate in part to the presence of platelet dysfunction and trace concentrations of circulating heparin during the postoperative period. Although aprotinin may offer advantages over the synthetic antifibrinolytic drugs in the form of platelet ''protection'' and serine protease inhibitory activity, a consensus regarding the optimal antifibrinolytic therapy for cardiac surgery must await more detailed cost benefit analyses.

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